

# The Origin and Early Evolution of Membrane Channels

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Although contemporary membrane channels are large and complex, their structural motifs are simple, with  $\alpha$ -helices being most common. This suggests that membrane proteins might have evolved from simple building blocks. To explain how these blocks could have organized into functional structures, we performed large-scale computer simulations of folding peptides at a water-membrane interface, their insertion into the membrane, self-assembly into higher-order structures and function. While the insertion of an  $\alpha$ -helix into a membrane is unfavorable, stability can be regained by specific recognition and association of peptides into larger assemblies. We argue that the transport of solute species, especially ions, required an early evolution of efficient transport mechanisms, and that the emergence of simple ion channels was protobiologically plausible. We also argue that, despite their simple structure, such channels could possess properties that, at the first sight, appear to require markedly larger complexity. These properties can be subtly modulated by local modifications to the sequence rather than global changes in molecular architecture. This is a convenient evolutionary solution because it does not require imposing conditions on the whole amino acid sequence. In order to address the evolution and development of ion channels, we identified protein domains that are commonly associated with ion channel proteins and are conserved throughout the three main domains of life. We argue that these domains have sufficiently universal architectures that they can readily adapt to the diverse functional demands arising during evolution.